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*Bij twijfel,
Altijd terug naar de bron.*

(Kuifje)



2

Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of south africa

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ABSTRACT

Tuberculous meningitis (TBM) is the most severe extrapulmonary complication of tuberculosis, with high morbidity and mortality rates. The objective of this study was to assess the relationship between presenting clinical characteristics and outcome of pediatric TBM.

We present a retrospective cohort study of all of the children diagnosed with TBM in a large university hospital in South Africa between January 1985 and April 2005. We compared demographic, clinical, and diagnostic characteristics with clinical outcome after 6 months of treatment.

We included 554 patients. Common characteristics on admission were young age (82%; <5 years), stage II or III TBM (97%), nonspecific symptoms existing for > 1 week (58%), poor weight gain or weight loss (91%), loss of consciousness (96%), motor deficit (63%), meningeal irritation (98%), raised intracranial pressure (23%), brainstem dysfunction (39%), and cranial nerve palsies (27%). Common features of TBM on computed tomography scan of the brain were hydrocephalus (82%), periventricular lucency (57%), infarctions (32%), and basal meningeal enhancement (75%). Clinical outcome after 6 months was as follows: normal (16%), mild sequelae (52%), severe sequelae (19%), and death (13%). All of the patients diagnosed with stage I TBM had normal outcome. Factors associated with poor outcome in univariate analyses were as follows: African ethnicity, young age, HIV co-infection, stage III TBM, absence of headache and vomiting, convulsions, decreased level of consciousness, motor deficits, cranial nerve palsies, raised intracranial pressure, brainstem dysfunction and radiographic evidence of hydrocephalus, periventricular lucency, and infarction. Ethnicity, stage of disease, headache, convulsions, motor function, brainstem dysfunction, and cerebral infarctions were independently associated with poor outcome in multivariate logistic regression analysis.

TBM starts with non-specific symptoms and is often only diagnosed when brain damage has already occurred. Earlier diagnosis will improve outcome significantly. We were able to identify presenting variables independently associated with poor clinical outcome.

BACKGROUND

Two billion people are infected with *Mycobacterium tuberculosis* (*M. tub*), and each year 9 million people develop tuberculosis (TB) [1]. Although the incidence of TB is increasing, prevalence and mortality rates are declining. Annually, ~2 million people die as a result of this disease [2].

Tuberculous meningitis (TBM) is the most severe complication of TB and frequently occurs in childhood. Lymphohematogenous spread from a primary pulmonary focus leads to the development of a *Rich focus* in the brain. Rupturing of this caseous granuloma into the subarachnoid space causes 3 features responsible for the clinical manifestations of TBM: development of further tuberculomas; basal inflammatory exudates that cause cranial nerve palsies and obstruct CSF pathways, resulting in hydrocephalus; and obliterative vasculitis, which leads to infarctions [3]. Once the *Rich focus* has ruptured, a prodromal period of nonspecific symptoms, such as fever, vomiting, and behavioral changes, develops. As the disease progresses, neck stiffness, loss of consciousness, motor deficits, and convulsions will follow. The diagnosis is often only considered once irreversible neurologic damage has already occurred [4].

The Western Cape Province has the highest incidence of TB in South Africa (998 per 100 000) and a 1.9% prevalence of HIV. HIV coinfection increases the risk of developing TBM and leads to more complications and a higher case fatality rate [5,6]. Incidence rates of TBM are age specific and range from 31.5 per 100 000 (< 1 year) to 0.7 per 100 000 (10–14 years) in the Western Cape Province [7].

PATIENTS AND METHODS

Study design

The objective of this study was to assess the relationship between presenting clinical characteristics and outcome of pediatric TBM. All of the children diagnosed with TBM at Tygerberg Hospital, a large university hospital in Cape Town, between January 1985 and April 2005, were included in this retrospective cohort study. We compared demographic, clinical, and diagnostic data on admission and clinical outcome after 6 months of treatment.

Demographic data

Demographic data include gender, race and age, HIV coinfection, Bacille Calmette-Guerin (BCG) immunization, and possible TB contact. We used the *Road-to-Health Card* for data collection. This is a record of immunizations and growth rate, widely used in South Africa to monitor the development of the child until he or she is 5 years old [8].

Diagnostic criteria

A definite diagnosis of TBM is made when *M. tub* is isolated from CSF. In all other cases, the diagnosis is “probable TBM” based on clinical signs of meningitis in the presence of characteristic CSF findings (macroscopically clear, pleocytosis, elevated protein, and reduced glucose). In addition, ≥ 2 of the following criteria have to be present: (1) recent poor weight gain (crossing of percentiles on *Road-to-Health Card*); (2) household contact with sputum smear-positive TB patient; (3) computed tomography (CT) scan compatible with TBM; (4) chest radiography compatible with primary TB; (5) positive tuberculin skin test; and (6) other clinical specimens positive for acid-fast bacilli.

Clinical data

We scored stage of disease, duration of symptoms before admission, type of presenting symptoms, nutritional state, Glasgow Coma Scale (GCS) score, motor function, and presence of other neurologic signs. TBM was staged using the modified criteria of the British Medical Research Council to determine the severity of TBM: stage I TBM (GCS 15 with no focal neurologic signs), stage II TBM (GCS 11–14 or GCS of 15 with focal neurologic deficit), and stage III TBM (GCS < 11) [9].

Motor function was classified as normal, left hemiparesis, right hemiparesis, quadriplegia, or other deficits. Other neurologic signs were meningeal irritation, signs of raised intracranial pressure (bulging fontanel, sun setting sign, and papill edema), signs of brainstem dysfunction (unequal or nonreactive pupils, absent oculocephalic reflex, decerebration, or neurogenic hyperventilation), and cranial nerve palsies.

Diagnostic data

Radiography

On CT scan images we scored hydrocephalus, expressed as the ratio between ventricular and bi-parietal diameters of the cerebral ventricles (*VP-ratio*), periventricular lucency (white matter changes because of hydrocephalus), basal meningeal enhancement, infarctions, and tuberculomas. Limited air encephalography was used to determine the level of CSF obstruction by injecting 5 to 10 mL of air into the lumbar CSF space during lumbar puncture. Air demonstrated in the ventricular system on a skull radiograph is indicative of communicating hydrocephalus (CH), whereas air trapped at the basal cisterns without entering the ventricles proves non-communicating hydrocephalus (NCH). Chest radiographic findings suggestive for TB include mediastinal lymphadenopathy, segmental infiltration and/or collapse, cavitation, or pleural effusion.

Microbiology

Isolation of *M. tub* from CSF makes a definite diagnosis of TBM. Isolation of *M. tub* from gastric aspirate, bronchial aspirate, sputum, or lymph node, combined with clinical suspicion of TBM, adds strongly to the diagnosis.

Tuberculin skin test

The *Mantoux* skin test is regarded positive as defined by guidelines of the World Health Organization: in high-risk children (including HIV-infected children and severely malnourished children), ≥ 5 mm of induration, and in all other children (whether they have received a BCG vaccination or not), ≥ 10 mm of induration [10].

Treatment of tuberculous meningitis

Cornerstones of TBM treatment are antimycobacterial drugs, immunomodulation, and management of hydrocephalus. We used an intensive short-course regimen of daily isoniazid (20 mg/kg), rifampicin (20 mg/kg), pyrazinamide (40 mg/kg), and ethionamide (20 mg/kg) for 6 months. Prednisone (2 mg/kg per day) was given for the first month of treatment and then gradually discontinued over the next 2 weeks. We treat NCH with a ventriculoperitoneal shunt (VPS) and CH with diuretics (50 mg/kg per day of acetazolamide and 1 mg/kg per day of furosemide). CH not responding to diuretics within 4 weeks is treated with a VPS [11].

Outcome of tuberculous meningitis

After completing 6 months of therapy, motor function, intelligence, vision, and hearing was tested. The Bayley test, Griffiths test, or Junior South African Individual Scale, depending on the age of the child, was used to measure IQ. Patients were grouped as “normal” (IQ: > 80), “mild intellectual impairment” (IQ: 50–80), or “severe intellectual impairment” (IQ: < 50). Vision and hearing were classified as normal, impaired vision or hearing, and blindness or deafness. We divided neurologic outcome into 4 categories: (1) normal, including normal motor function, intelligence, vision, and hearing; (2) mild sequelae, including hemiparesis, mild intellectual impairment, and impaired vision and/or hearing; (3) severe sequelae, including quadriplegia, severe intellectual impairment, blindness, and/or deafness; and (4) death. Clinical outcome was defined as “good” in the case of mild neurologic sequelae or normal neurologic outcome and defined “poor” in the case of severe neurologic sequelae or death.

Statistical analyses

SPSS 13.0 (SPSS Inc, Chicago, IL) has been used for statistical analyses. Statistical significance was determined at the 5% level. We used the χ^2 test and relative risks in univariate analyses to determine which variables were associated with poor clinical

outcome. To study the independent effect of variables, we used multivariate logistic regression analysis. All of the variables with a P -value of < 0.2 were included one by one in a multivariate logistic regression model, starting with the variables with the smallest P -value. Different models were made, with and without variables, with high percentages of missing values. All of the variables with a P -value of < 0.2 were kept in the model. We calculated the area under the curve (AUC) as a measure of the discriminative ability to distinguish between patients with good and poor outcome. An AUC of ≥ 0.7 is generally considered to be adequate. The ethical committee of the University of Stellenbosch Faculty of Health Sciences approved this study.

RESULTS

Demographic data

Boys and girls were equally affected (*Table 1*). TBM has a higher incidence in the African and Colored population of South Africa. Most of the children were very young ($82\% < 5$ years of age).

Clinical data

Most patients had stage II or III TBM and had nonspecific symptoms existing for > 1 week (*Table 2*). On admission, the majority of patients had poor weight gain, decreased level of consciousness, and any type of motor deficit. Meningeal irritation was present in 98% and signs of raised intracranial pressure in 23% of patients. Thirty-nine percent of patients had ≥ 1 sign of brainstem dysfunction. Cranial nerve palsies occurred in 27% of children.

Diagnostic data

Hydrocephalus was often present, as indicated by abnormal *VP-ratios* (*Tables 3 and 4*). Periventricular lucency and basal meningeal enhancement were found in $> 50\%$ of patients. Tuberculomas were found in a minority of patients. Eighty-three percent of patients underwent limited air encephalography, demonstrating that CH occurred twice as often as NCH. Chest radiography results often showed abnormalities suspect for TB. Culture for *M. tub* was from any type of origin was positive in 30%; in only 12% of patients *M. tub* was isolated from the CSF. The tuberculin skin test was positive in 60% of patients. Lymphocyte counts and protein levels in CSF were elevated, and the CSF/blood glucose ratio was reduced.

Table 1. Demographic data

Variable	Data	Association With Poor Outcome ^a
Gender	<i>n</i> = 553 ^b	<i>n</i> = 412 ^c
Male, <i>n</i> , %	290, 52.4	RR: 1.0 (CI:0.7-1.3); <i>P</i> = .96
Female, <i>n</i> , % ^d	263, 47.6	
Race	<i>n</i> = 552 ^b	<i>n</i> = 412 ^c
African, <i>n</i> , %	113, 20.5	RR:1.5 (CI:1.1-2.0); <i>P</i> = .02
Black (mixed), <i>n</i> , % ^d	439, 79.5	
European and Asian, <i>n</i> , %	0, 0.0	
Age on admission	<i>n</i> = 546 ^b	<i>n</i> = 409 ^c
Median and range	28 mo (2-180)	
0-1 y, <i>n</i> , %	108, 19.8	RR: 2.9 (CI: 1.6-5.6); <i>P</i> <.001
1-2 y, <i>n</i> , %	129, 23.6	RR: 3.0 (CI: 1.6-5.5); <i>P</i> <.001
2-5 y, <i>n</i> , %	209, 38.3	RR: 1.9 (CI: 1.0-.6); <i>P</i> = .03
>5 y, <i>n</i> , % ^d	100, 18.3	
HIV infection	<i>n</i> = 213 ^b	<i>n</i> = 188 ^c
Positive, <i>n</i> , %	8, 3.8	RR: 2.3 (CI: 1.2-4.2); <i>P</i> = .05
Negative, <i>n</i> , % ^d	205, 96.2	
BCG documented	<i>n</i> = 244 ^b	<i>n</i> = 199 ^c
Yes, <i>n</i> , % ^d	236, 96.7	
No, <i>n</i> , %	8, 3.3	RR: 1.4 (CI:0.6-3.4); <i>P</i> = .50
BCG scar	<i>n</i> = 488 ^b	<i>n</i> = 390 ^c
Yes, <i>n</i> , % ^d	136, 27.9	
No, <i>n</i> , %	352, 72.1	RR: 1.0 (CI: 0.7-1.4); <i>P</i> = .94
TB contact	<i>n</i> = 554 ^b	<i>n</i> = 412 ^c
Known, <i>n</i> , %	295, 53.2	RR: 0.9 (CI: 0.7-1.2); <i>P</i> = .57
Unknown, <i>n</i> , % ^d	259, 46.8	

RR indicates relative risk; CI, 95% confidence interval; *P*, *P* value of χ^2 test.

^a Data indicate poor outcome: death or severe sequelae (quadriplegia, severe intellectual impairment, blindness, and/ or deafness).

^b Variable is known for this number of patients.

^c Variable and outcome are known for this number of patients.

^d Data show the reference group.

Table 2. Clinical data on admission

Variable	Data	Association With Poor Outcome ^a
TBM staging	<i>n</i> = 548 ^b	<i>n</i> = 406 ^c
Stage I, <i>n</i> , %	14, 2.6	No poor outcome in stage I
Stage II, <i>n</i> , % ^d	314, 57.3	
Stage III, <i>n</i> , %	220, 40.1	RR: 4.0 (CI: 2.9-5.5); <i>P</i> < .001
Duration of symptoms	<i>n</i> = 530 ^b	<i>n</i> = 395 ^c
Median and range, d	9 (1-122)	
0-7 d, <i>n</i> , %	225, 42.5	RR: 1.0 (CI: 0.6-1.5); <i>P</i> = .84
8-14 d, <i>n</i> , %	168, 31.7	RR: 0.9 (CI: 0.6-1.4); <i>P</i> = .60
15-21 d, <i>n</i> , %	78, 14.7	RR: 0.8 (CI: 0.4-1.3); <i>P</i> = .34
>21 d, <i>n</i> , % ^d	59, 11.1	
Presenting symptoms	<i>n</i> = 509 ^b	<i>n</i> = 385 ^c
Decreased consciousness, <i>n</i> , %	356, 69.9	RR: 1.3 (CI: 0.9-2.0); <i>P</i> = .12
Fever, <i>n</i> , %	339, 66.6	RR: 0.9 (CI: 0.6-1.2); <i>P</i> = .34
Vomiting, <i>n</i> , %	269, 52.8	RR: 0.6 (CI: 0.4-0.8); <i>P</i> = .001
Malaise, <i>n</i> , %	263, 51.7	RR: 0.9 (CI: 0.7-1.2); <i>P</i> = .54
Convulsion, <i>n</i> , %	240, 47.2	RR: 1.8 (CI: 1.3-2.4); <i>P</i> < .001
Weight loss, <i>n</i> , %	236, 46.4	RR: 0.9 (CI: 0.7-1.3); <i>P</i> = .70
Cough, <i>n</i> , %	164, 32.2	RR: 1.1 (CI: 0.8-1.6); <i>P</i> = .38
Weakness, <i>n</i> , %	157, 30.8	RR: 1.2 (CI: 0.9-1.7); <i>P</i> = .19
Headache, <i>n</i> , %	128, 25.1	RR: 0.4 (CI: 0.3-0.7); <i>P</i> < .001
Nutritional state	<i>n</i> = 232 ^b	<i>n</i> = 186 ^c
Consistent weight gain, <i>n</i> , % ^d	22, 9.5	
Poor weight gain, <i>n</i> , %	106, 45.7	RR: 3.0 (CI: 0.8-11.2); <i>P</i> = .06
Weight loss, <i>n</i> , %	104, 44.8	RR: 2.5 (CI: 0.7-9.8); <i>P</i> = .13
GCS	<i>n</i> = 553 ^b	<i>n</i> = 412 ^c
Median and range, <i>n</i> , %	10 (3-15)	
15, <i>n</i> , % ^d	22, 4.0	
12-14, <i>n</i> , %	217, 39.2	RR: 2.0 (CI: 0.3-13.8); <i>P</i> = .48
9-11, <i>n</i> , %	120, 21.7	RR: 5.0 (CI: 0.7-34.2); <i>P</i> = .04
≤8, <i>n</i> , %	194, 35.1	RR: 10.0 (CI: 1.5-67.0); <i>P</i> < .001
Motor function	<i>n</i> = 554 ^b	<i>n</i> = 408 ^c
Normal, <i>n</i> , % ^d	204, 36.8	
Left hemiparesis, <i>n</i> , %	107, 19.3	RR: 1.6 (CI: 0.8-3.1); <i>P</i> = .15
Right hemiparesis, <i>n</i> , %	99, 17.9	RR: 3.9 (CI: 2.3-6.6); <i>P</i> < .001
Quadriplegia, <i>n</i> , %	138, 24.9	RR: 5.9 (CI: 3.6-9.6); <i>P</i> < .001

Other (mono/paraparesis), <i>n</i> ,%	6, 1.1	RR: 2.3 (CI: 0.4-13.2); <i>P</i> = .38
Meningeal irritation	<i>n</i> = 460 ^b	Too small number (<i>n</i> = 3) of patients followed up with absence of meningeal irritation on admission to test association with poor outcome
Present, <i>n</i> ,%	445, 98.1	
Absent, <i>n</i> ,%	15, 1.9	
Raised intracranial pressure	<i>n</i> = 552 ^b	<i>n</i> = 412 ^c
Present, <i>n</i> ,%	125, 22.6	RR: 1.7 (CI: 1.2-2.2); <i>P</i> = .002
Absent, <i>n</i> ,% ^d	427, 77.4	
Brainstem dysfunction	<i>n</i> = 554 ^b	<i>n</i> = 412 ^c
Present, <i>n</i> ,%	214, 38.6	RR: 3.0 (CI: 2.2-4.1); <i>P</i> < .001
Absent, <i>n</i> ,% ^d	340, 61.4	
Cranial nerve palsies	<i>n</i> = 541 ^b	<i>n</i> = 400 ^c
Present, <i>n</i> ,%	145, 26.8	RR: 1.5 (CI: 1.1-2.0); <i>P</i> = .01
Absent, <i>n</i> ,% ^d	396, 73.2	

RR indicates relative risk; CI, 95% confidence interval; *P*, *P* value of χ^2 test.

^a Data indicate poor outcome: death or severe sequelae (quadriplegia, severe intellectual impairment, blindness, and/or deafness).

^b Variable is known for this number of patients.

^c Variable and outcome are known for this number of patients.

^d Data show the reference group.

Treatment of tuberculous meningitis

All 554 of the children received antimycobacterial drugs, and 68% received corticosteroids (*Table 5*). The majority of children with CH were treated with diuretics only (75%). Patients with CH not responding to diuretic treatment within a month received a VPS (18%).

Outcome

Only a small group of children (16%) was not affected by TBM (*Table 6*). Vision was affected in 14% and hearing in 16% of the children. A large group of children had motor deficits (44%) and intellectual impairment (77%). The deceased children died of cerebral herniation, infarction, cardio-respiratory arrest, shunt infection/obstruction, or pneumonia.

In a previous study, which described a subgroup of the current study population, we reported that we could not associate mycobacterial genotype with clinical characteristics and outcome of TBM [12]. From other studies we know that there is no evidence for strain-specific central nervous system tropism in humans [13].

Table 3. Diagnostic data on admission

Variable	Data	Association With Poor Outcome ^a
CT: VP ratio	<i>n</i> = 237 ^b	<i>n</i> = 223 ^c
Mean and range	0.24 (0.08-0.53)	
Abnormal: VP ratio >0.200, <i>n</i> , %	165, 69.6	RR: 1.4 (CI: 0.8-2.2); <i>P</i> = .19
Normal: VP ratio ≥0.200, <i>n</i> , % ^d	72, 30.4	
CT: periventricular lucency	<i>n</i> = 515 ^b	<i>n</i> = 393 ^c
Present, <i>n</i> , %	292, 56.7	RR: 1.5 (CI: 1.1-2.1); <i>P</i> = .01
Absent, <i>n</i> , % ^d	223, 43.3	
CT: infarctions	<i>n</i> = 516 ^b	<i>n</i> = 394 ^c
Present, <i>n</i> , %	164, 31.8	RR: 2.2 (CI: 1.6-2.9); <i>P</i> < .001
Absent, <i>n</i> , % ^d	352, 68.2	
CT: basal meningitis enhancement	<i>n</i> = 517 ^b	<i>n</i> = 394 ^c
Present, <i>n</i> , %	387, 74.9	RR: 1.2 (CI: 0.8-1.7); <i>P</i> = .40
Absent, <i>n</i> , % ^d	130, 25.1	
CT: tuberculomas	<i>n</i> = 509 ^b	<i>n</i> = 386 ^c
Present, <i>n</i> , %	66, 13.0	RR: 1.1 (CI: 0.7-1.6); <i>P</i> = .83
Absent, <i>n</i> , % ^d	443, 87.0	
Chest radiography	<i>n</i> = 536 ^b	<i>n</i> = 404 ^c
Miliary tuberculosis, <i>n</i> , %	66, 12.3	RR: 1.4 (CI: 0.9-2.1); <i>P</i> = .12
Other abnormalities, <i>n</i> , %	249, 46.5	RR: 1.2 (CI: 0.9-1.6); <i>P</i> = .32
Normal, <i>n</i> , % ^d	221, 41.2	
Air encephalography	<i>n</i> = 553 ^b	<i>n</i> = 402 ^c
Communicating, <i>n</i> , %	310, 57.5	RR: 4.3 (CI: 2.0-9.4); <i>P</i> < .001
Noncommunicating, <i>n</i> , %	135, 25.0	RR: 3.5 (CI: 1.6-8.0); <i>P</i> = .001
No hydrocephalus, <i>n</i> , % ^d	94, 17.4	
Culture	<i>n</i> = 554 ^b	<i>n</i> = 412 ^c
Positive from CSF, <i>n</i> , %	64, 11.7	RR: 0.9 (CI: 0.5-1.4); <i>P</i> = .57
Positive from other origin, <i>n</i> , %	104, 18.6	RR: 1.1 (CI: 0.8-1.6); <i>P</i> = .48
Negative/not tested, <i>n</i> , % ^d	386, 69.7	
Mantoux test	<i>n</i> = 500 ^b	<i>n</i> = 380 ^c
Positive, <i>n</i> , %	304, 60.8	RR: 0.9 (CI: 0.6-1.2); <i>P</i> = .39
Negative, <i>n</i> , % ^d	196, 39.2	

Legend to table 3

RR indicates relative risk; CI, 95% confidence interval; *P*, *P* value of χ^2 test, V, ventricular diameter at midportion of the lateral ventricles; P, biparietal diameter from inner table to inner table.

^a Data indicate poor outcome: death or severe sequelae (quadriplegia, severe intellectual impairment, blindness, and/or deafness).

^b Variable is known for this number of patients.

^c Variable and outcome are known for this number of patients.

^d Data show the reference group.

Table 4. CSF Findings on admission

Variable	Data	Association With Poor Outcome ^a
Lymphocytes	<i>n</i> = 514 ^b	<i>n</i> = 386 ^c
Median of range, cells per μL	97 (0-1213)	
Normal: 0-10 cells per μL , <i>n</i> , % ^d	50, 9.7	
Abnormal: >10 cells per μL , <i>n</i> , %	464, 90.3	RR: 0.9 (CI: 0.5-1.3); <i>P</i> = .52
Polymorph leukocytes	<i>n</i> = 512 ^b	
Median of range, cells per μL	10 (0-684)	
Protein	<i>n</i> = 504 ^b	<i>n</i> = 377 ^c
Median of range	1.6 g/L (0.1-109.0)	
Normal: ≤ 0.8 g/L, <i>n</i> , % ^d	85, 16.9	
Abnormal: >0.8 g/L, <i>n</i> , %	419, 83.1	RR: 1.2 (CI: 0.8-1.9); <i>P</i> = .45
Glucose in serum	<i>n</i> = 171 ^b	<i>n</i> = 123 ^c
Median of range, mmol/L	6.2 (2.0-21.7)	
Normal: 3.3-7.8 mmol/L, <i>n</i> , % ^d	141, 81.5	
Abnormal: <3.3 mmol/L, <i>n</i> , %	2, 1.2	RR: 1.5 (CI: 1.0-2.4); <i>P</i> = .34
Abnormal: >7.8 mmol/L, <i>n</i> , %	30, 17.2	Abnormal groups are combined together
Glucose in CSF	<i>n</i> = 471 ^b	
Median of range, mmol/L	1.7 (0.0-8.6)	
CSF/blood glucose ratio	<i>n</i> = 172 ^b	<i>n</i> = 122 ^c
Median of range, %	26 (0-92)	
Normal: 60%-80% <i>n</i> , % ^d	10, 5.8	
Abnormal: <60%, <i>n</i> , %	159, 92.5	RR: 0.9 (CI: 0.3-2.8); <i>P</i> = .83
Abnormal: >80%, <i>n</i> , %	3, 1.7	Abnormal groups are combined together

RR indicates relative risk; CI, 95% confidence interval; *P*, *P* value of χ^2 test.

^a Data indicate poor outcome: death or severe sequelae (quadriplegia, severe intellectual impairment, blindness, and/or deafness).

^b Variable is known for this number of patients.

^c Variable and outcome are known for this number of patients.

Table 5. Treatment of TBM

Variable	Data	Association With Poor/Fatal Outcome ^a
Antimycobacterial drugs	<i>n</i> = 554 ^b	
Yes, <i>n</i> , %	554, 100.0	
No, <i>n</i> , %	0, 0.0	
Treatment of hydrocephalus	<i>n</i> = 409 ^c	
Communicating	<i>n</i> = 310 ^b	
Diuretics, <i>n</i> , %	233, 75.3	RR: 3.3 (CI: 1.5-7.3); <i>P</i> = .001
Diuretics and shunt, <i>n</i> , %	56, 18.0	RR: 6.8 (CI: 3.0-15.3); <i>P</i> < .001
No treatment, <i>n</i> , % ^d	21, 6.8	RR: ∞; only poor outcome
Non-communicating	<i>n</i> = 135 ^b	
Shunt, <i>n</i> , %	122, 90.4	RR: 3.5 (CI: 1.6-8.0); <i>P</i> = .001
Diuretics, <i>n</i> , % ^e	11, 8.1	RR: 1.6 (CI: 0.2-11.6); <i>P</i> = .64
No treatment, <i>n</i> , % ^d	2, 1.5	RR: ∞; only poor outcome
No hydrocephalus	<i>n</i> = 94 ^b	
No treatment, <i>n</i> , % ^f	94, 100.0	
Corticosteroids	<i>n</i> = 554 ^b	<i>n</i> = 412 ^c
Yes, <i>n</i> , % ^f	374, 67.5	
No, <i>n</i> , %	180, 32.5	Poor outcome: RR: 1.2 (CI: 0.8-1.6); <i>P</i> = .39
		Fatal outcome: RR: 2.5 (CI: 1.7-3.7); <i>P</i> < .001

RR indicates relative risk; CI, 95% confidence interval; *P*, *P* value of χ^2 test.

^a Data indicate poor outcome: death or severe sequelae (quadriplegia, severe intellectual impairment, blindness, and/ or deafness).

^b Variable is known for this number of patients.

^c Variable and outcome are known for this number of patients.

^d Data show children with severe brain damage on admission who did not receive treatment for their hydrocephalus because it would not improve their outcome.

^e Data include 11 children with NCH, and open fontanelles were treated with diuretics because intracranial pressure [ICP] could be monitored clinically. Five of these children received a shunt after 1 month, because treatment with only diuretics was not successful..

^f Data show the reference group.

Table 6. Outcome at follow-up after 6 months of treatment

Variable	Data
Vision ^a	<i>n</i> = 374 ^b
Normal, <i>n</i> , %	322, 86.1
Loss of vision, <i>n</i> , %	20, 5.3
Blindness, <i>n</i> , %	32, 8.6
Hearing ^a	<i>n</i> = 348 ^b
Normal, <i>n</i> , %	292, 83.9
Loss of hearing, <i>n</i> , %	55, 15.8
Deafness, <i>n</i> , %	1, 0.3
Motor functions ^a	<i>n</i> = 450 ^b
Normal, <i>n</i> , %	254, 56.4
Left hemiparesis, <i>n</i> , %	73, 16.3
Right hemiparesis, <i>n</i> , %	59, 13.1
Quadriparesis, <i>n</i> , %	60, 13.3
Other deficits, <i>n</i> , %	4, 0.9
IQ ^a	<i>n</i> = 359 ^b
Mean and range	64 (2-116)
Normal: <80, <i>n</i> , %	82, 22.8
Mild impairment: 50-80, <i>n</i> , %	207, 57.7
Severe impairment: <50, <i>n</i> , %	70, 19.5
Total outcome	<i>n</i> = 359 ^b
Normal, <i>n</i> , %	65, 15.8
Mild sequelae, <i>n</i> , %	217, 52.6
Severe sequelae, <i>n</i> , %	77, 18.7
Death, <i>n</i> , %	53, 12.9
Time admission to death ^d	<i>n</i> = 51 ^b
Median of range, days	23 (2-1466)
0-7, <i>d</i> , <i>n</i> , %	14, 27.5
8-30, <i>d</i> , <i>n</i> , %	15, 29.4
30-90, <i>d</i> , <i>n</i> , %	10, 19.6
>90, <i>d</i> , <i>n</i> , %	12, 23.5

^a After 6 months, 53 children died; the maximum amount of children at follow-up is 501.

^b Variable is known for this number of patients.

^c The outcome is determined by the combination of motor functions, IQ scores, vision, and hearing (for 98 children, vision and/or hearing is unknown).

^d At follow-up, 53 children died; 4 other children died after >6 months. For 51 children, the exact date of death is known.

Prediction of poor outcome

Associated with poor outcome in the univariate analyses are African ethnicity, young age, HIV coinfection, stage III TBM, absence of headache, absence of vomiting, convulsions, decreased consciousness, motor deficits, raised intracranial pressure, brainstem dysfunction, cranial nerve palsies, periventricular lucency, cerebral infarctions, and hydrocephalus (*Tables 1–5 and 7*). The absence of corticosteroids in TBM treatment was associated with fatal outcome in this study for all stages of disease. We did not find a threshold of days after which corticosteroids were no longer effective. However, we found lower mortality with corticosteroids but not a better clinical outcome: the patients survived but with severe neurologic sequelae.

In multivariate analyses, slightly different models were found depending on the variables that were entered first in the models and the inclusion or exclusion of variables with missing values. Seven variables entered all of the models and were included in the final model to predict poor clinical outcome. These were race, stage of disease, convulsions, headache, motor functions, brainstem dysfunction, and cerebral infarctions, as shown in *Table 7*. The AUC of the model was 0.84 (95% confidence interval: 0.80–0.89).

DISCUSSION

This study confirms that TBM mainly affects young children, because 82% of our cohort was < 5 years of age. The mean age of 37 months is comparable to other studies, with mean ages ranging from 23 to 49 months [14–18]. Young age at presentation and the nonspecific nature of presenting symptoms partly explain the difficulty of early

Table 7. Multivariable Logistic Regression Analysis

Variable	Odds Ratio, 95% Confidence Interval	P
Race ^a	2.6, 1.3–5.4	.008
Stage ^b	4.8, 2.7–8.7	<.001
Convulsion	1.5, 0.8–2.6	.07
Headache	2.0, 0.9–4.2	.18
Motor functions ^c	1.8, 0.9–3.7	.10
Brainstem dysfunction	2.9, 1.6–5.1	<.001
Infarctions on CT scan	2.6, 1.4–4.6	.001

^a Data show African versus Colored.

^b Data show stage III versus stage I or II.

^c Data show any type of motor deficit versus normal.

diagnosis. Presentation is often subacute, and the early symptoms of stage I TBM, such as low-grade fever, cough, vomiting, and general apathy, are often wrongly interpreted [19]. This delay in diagnosis and start of TB treatment are supported by the finding that 57% of our cohort were unwell for > 7 days before admission. We demonstrated previously that missed opportunities for early diagnosis rather than late presentation or inaccessibility to medical care are the most common cause for delayed diagnosis of childhood TBM [20]. According to the literature, the duration of symptoms before diagnosis of TBM ranges between 13 and 42 days [16,18,21-23].

Recent poor weight gain is a valuable clue to early diagnosis of pediatric TBM in areas where TB is endemic [8]. This observation is confirmed by the present study, which showed that 90% of patients had either weight loss or poor weight gain for weeks to months before presentation.

Once TBM progresses to stage II and III disease, neck stiffness will almost always be present, as was the case in 98% of our patients. The CSF results in our patients emphasize that the majority of patients with TBM will have a low, predominantly lymphocyte CSF pleocytosis in the presence of a raised protein level and reduced CSF/blood glucose ratio. These CSF findings, especially if culture negative, are highly suggestive of TBM in areas with a high prevalence rate of TB. We have shown previously that as many as 11% of TBM patients are wrongly treated for bacterial meningitis on account of the results of the first lumbar puncture [20]. CSF changes in TBM take long to normalize, and serial CSF findings may, therefore, retrospectively differentiate TBM from other types of meningitis where the CSF normalizes much quicker [24].

The prevention of TBM is as important as early diagnosis. Fifty-three percent of our patients had contact with a household adult with proven pulmonary TB, which is comparable with the 51% to 69% reported rates of other studies [14-18,23]. Undiagnosed and untreated TB is considered an important risk factor in the spread of the disease and the development of TBM. A history of close contact with a patient with proven TB is important in early diagnosis of TBM, especially at the stage when only nonspecific symptoms are present.

Delayed treatment of TBM because of missed diagnosis will result in progression to stage II and III disease with high morbidity and mortality rates. In our study, only 16% of patients did not have sequelae, 71% had any type of sequelae, and 13% of the children died as a consequence of TBM. This agrees with other studies in the literature, which showed normal outcome in 11% to 61%, sequelae in 13% to 75%, and death in 7% to 57% [14-18,21-23]. The poor outcome found in TBM patients who were HIV coinfectd (25% mortality and 25% severe sequelae) in this study is in agreement with the literature.

Corticosteroids reduce mortality but do not significantly alter the long-term sequelae of TBM. Children who would otherwise die without corticosteroids will now

survive with severe sequelae. The benefit of corticosteroids in TBM is proven by several studies, but the mechanism is unknown. Corticosteroids do reduce brain edema and might reduce cytokine production and subsequent brainstem encephalopathy. The adjuvant treatment with corticosteroids in these studies led to improved survival but not to a decrease in motor deficits [25-27].

It is impossible to determine the role of possible multidrug-resistant (MDR) tuberculosis on the outcome of our patients, because only 12% were culture positive, and drug resistance testing was not routinely done. Selective drug resistance testing, however, showed that MDR in our hospital-based childhood population is ~12% and has not changed significantly over the last decade [28].

The optimal length of therapy in TBM has not been established, because there are no data from randomized controlled trials. We treated patients with TBM for 6 months. The basis of our regimen is a prospective study published in 1998 [29]. We are aware of other recommendations advising treatment up to 9 or 12 months [30,31]. World Health Organization guidelines for national programs advise an intensive phase of treatment with isoniazid, rifampicin, pyrazinamide, and streptomycin for 2 months and a continuation phase with the first 2 drugs for 4 months. They consider our 6-month regimen with ethionamide instead of streptomycin as an adequate alternative [10].

Hydrocephalus is a common complication of TBM, occurring in 57% to 99% of patients [15-18]. We found hydrocephalus, diagnosed as a VP ratio of > 0.2 , in 70% of patients. Although modern neuroimaging has improved the diagnosis of tuberculous hydrocephalus significantly, the literature regarding its management is confusing. Over the past 20 years, we based the treatment on the level of CSF block determined by limited air encephalography, as described by Lorber [32]. We resorted to this technique because modern neuroimaging, including CT and magnetic resonance imaging (MRI) of the brain, does not differentiate between CH (basal cistern block) and NCH (fourth ventricular outlet obstruction), because both cause panventricular dilatation. This study confirms our previous observation that only ~25% of patients with tuberculous hydrocephalus have NCH with a risk for herniation and are in need of an emergency VPS. The rest have CH, which generally responds well to a trial of diuretic therapy, as did 75% of patients in the present study. Hydrocephalus that does not become compensated within a month on medical treatment is treated with a VPS. This approach to the management of tuberculous hydrocephalus has many obvious advantages in a resource-poor setting. These not only include huge cost savings but also decreased patient morbidity and mortality. Shunt obstruction in a shunt-dependent child may be fatal because of limited access to neurosurgical services in rural areas. We showed previously that clinical outcome in patients who were

immediately shunted for tuberculous hydrocephalus and those first treated medically did not differ significantly [11].

Our mortality rate of 13% is exceptionally low. This could be explained by a number of factors, including directly observed therapy, active treatment of hydrocephalus, and low rate of HIV coinfection and MDR TB in our population. However, the very high morbidity rate (only 16% had normal outcome) emphasizes the importance of stage of disease when treatment is begun. Most factors found to correlate with poor outcome in TBM can be directly traced to the degree of disease progression at the time of diagnosis. This applies to both clinical and radiologic characteristics of the disease. This dismal outcome of TBM will only improve when the diagnosis and initiation of treatment are made earlier. All of our patients with stage I disease had normal neurologic outcome, and deaths did not occur in this group.

CONCLUSIONS

TBM affects mainly children < 5 years of age. Presentation is often subacute, and early symptoms are non-specific. Recent poor weight gain, low-grade fever, vomiting, and recent contact with a TB patient are important clues for an early diagnosis of TBM. Outcome is directly associated with the stage of TBM. Delayed treatment because of missed diagnosis will result in progression to stage II and III disease with high morbidity and mortality rates. In multivariate analyses, we could identify several presenting variables independently associated with poor clinical outcome of TBM.

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